

Heritability of proliferative diabetic retinopathy

Kustaa Hietala, MD, Carol Forsblom, MD DMSc, Paula Summanen, MD DMSc, Per-Henrik Groop, MD DMSc, on behalf of the FinnDiane Study Group

Folkhälsan Institute of Genetics, Folkhälsan Research Center, Biomedicum Helsinki, Finland (KH, CF, P-HG); Department of Ophthalmology, Helsinki University Central Hospital, Finland (KH, PS); Division of Nephrology, Department of Medicine, Helsinki University Central Hospital, Finland (CF, P-HG)

Address for correspondence: Per-Henrik Groop, MD DMSc
Folkhälsan Research Center
Biomedicum Helsinki
Haartmaninkatu 8
POB 63, FIN-00014 University of Helsinki, Finland
Email: per-henrik.groop@helsinki.fi

Received for publication 22 October 2007 and accepted in revised form 22 April 2008.

Additional information for this article can be found in an online appendix at
<http://diabetes.diabetesjournals.org>.

Objective: Diabetic nephropathy clusters in families suggesting that genetic factors play a role in its pathogenesis. We investigated whether similar clustering exists for proliferative retinopathy in families with two or more siblings with type 1 diabetes.

Research design and methods: The FinnDiane Study has characterized 20% (4800 patients) of adults with type 1 diabetes in Finland. In 188 families there were at least two siblings with type 1 diabetes. Ophthalmic records were obtained for 369/396 (93%) and fundus photographs for 251/369 (68%) patients. Retinopathy was graded based on photographs and/or repeated ophthalmic examinations using the ETDRS-grading scale.

Results: Mean age at onset of diabetes was 14.3 (\pm 10.2) years and mean duration 25.9 (\pm 11.8) years. Proliferative retinopathy was found in 115/369 patients (31%). The familial risk of proliferative retinopathy was estimated in 168/188 sibships, adjusted for HbA_{1c}, duration and mean blood pressure. Proliferative retinopathy in the probands (48/168) was associated with an increased risk (Odds Ratio [OR] 2.76 [95% CI 1.25- 6.11], P=0.01) of proliferative retinopathy in the siblings of probands (61/182). The heritability of proliferative retinopathy was $h^2=0.52$ (\pm 0.31, P<0.05).

Conclusions: We found a familial clustering of proliferative retinopathy in patients with type 1 diabetes. The observation cannot be accounted for by conventional risk factors, suggesting a genetic component in the pathogenesis of proliferative retinopathy in type 1 diabetes.

Diabetic nephropathy and proliferative retinopathy are severe microvascular complications of diabetes. Diabetic nephropathy clusters in families suggesting that genetic factors play a role in the pathogenesis of this complication (1). However, there is yet no evidence for a similar clustering of proliferative retinopathy in families with type 1 diabetes.

After 20 years of diabetes almost all patients with type 1 diabetes and 58% of patients with type 2 diabetes show signs of retinopathy. When retinopathy worsens, severe visual loss eventually threatens 5-10% of the patients (2). The most severe form of retinopathy is proliferative retinopathy and most of the patients with this complication will become blind after 5-10 years without treatment (3). The prevalence of proliferative retinopathy varies between 13 and 50% after 15-20 years of diabetes duration in patients needing insulin (2;4).

The prevalence of any retinopathy is strongly related to the duration and the glucose exposure (2;4). Furthermore, poor glycemic control increases the incidence and progression of retinopathy (5;6). Nevertheless, glycemic exposure seems to explain only a part of the risk of proliferative retinopathy (7). In patients with type 2 diabetes, high blood pressure increases the incidence of retinopathy (8). It is noteworthy, that proliferative retinopathy is associated with diabetic nephropathy, a complication that is at least in part genetically determined (2). Such an association suggests that familial factors may also contribute to the development of proliferative retinopathy.

Therefore, the aim of this study was to elucidate whether there is a familial clustering of proliferative retinopathy in patients with longstanding type 1 diabetes and to estimate the degree of familiarity by calculating the heritability of proliferative retinopathy.

RESEARCH DESIGN AND METHODS

The present study was undertaken as part of the ongoing FinnDiane Study (Finnish Diabetic Nephropathy Study), a nationwide multi-center project with the aim to identify genetic and environmental risk factors for diabetic complications in type 1 diabetes. The protocol is in accordance with the Declaration of Helsinki, and was approved by the ethics committee of the Helsinki University Central Hospital.

The FinnDiane Study has to date recruited 4800 patients with type 1 diabetes. All patients who visit any of the participating 92 hospitals and health care centers are given an opportunity to take part in the FinnDiane Study. The response rate has been 78% (9). Although FinnDiane is not a population based study in the strict sense, the distribution of the patients closely follows the distribution of the general population in Finland. As a part of the baseline visit patients answered a question whether any of their close relatives had type 1 diabetes, as defined by having an age at onset of 40 years or less and insulin treatment initiated within one year of the diagnosis. With these criteria, 188 families with at least two siblings with type 1 diabetes were found (Table 1). All the siblings were contacted and those siblings, who agreed to take part, signed a consent form and were characterized at a FinnDiane center. Data on medication, cardiovascular status, diabetic complications, hypertension and cardiovascular disease were obtained using a standardised questionnaire, which was completed by the patient's attending physician. Blood pressure was measured twice in the sitting position using a mercury sphygmomanometer after a rest of at least 10 min. Anthropometric data, such as height and weight were recorded, and blood was drawn for the laboratory measurements, including HbA_{1c}.

We were able to obtain ophthalmic records and/or fundus photographs for a total of 369/396 (93 %) patients. Photographs were

available for 251/369 (68%) of these patients, and records of repeated fundus examinations performed by a specialist in ophthalmology for 332/369 (90%) patients. Both were available for 217/369 (59%) patients. Those patients with images available (68 %) had been photographed on a median of 3 separate times (IQR 1-5). For 34/369 (9%) patients the only source of information was the screening photographs taken at the local health canter. A diabetologist's evaluation of the fundi was the only source of information for only 3/369 (1%) of the patients, all of whom had mild diabetic retinopathy. All available patient data were used to score the severity and progression of retinopathy, a procedure handled by an ophthalmologist unaware of the demographic data and the presence or absence of other complications. The ETDRS-grading scale (Early Treatment of Diabetic Retinopathy) was used, where 10 represents no retinopathy, 61 and upwards proliferative retinopathy and 80 advanced retinopathy.(10) Patients without photographs were assigned a most probable estimate of ETDRS-score based on the descriptions of repeated fundus examinations. The eye with the more severe retinopathy was used to define the severity of retinopathy of the patient.

Patient's nephropathy status was classified according to their urinary albumin excretion rate (AER) in at least 2 out of 3 overnight or 24-h urine collections. Normal AER was defined as an AER < 20 µg /min or AER < 30 mg/24-h, microalbuminuria as an AER ≥ 20 and < 200 µg/min or ≥ 30 and < 300 mg/24 h, macroalbuminuria as an AER ≥ 200 µg/min or ≥ 300 mg/24 h, and end-stage renal disease when the patient required dialysis or renal transplantation.

Statistical analysis. The siblings were ranked by age and the oldest sibling was designated as the proband of each sibship. There were four twin pairs from four different families and the sibling with the longest duration of

diabetes was chosen as the proband in these particular sibships. Two twin pairs were monozygotic as determined by microsatellite markers (ABI MD-10 V2.5, Applied Biosystems, CA).

Data are presented as means and standard deviations (\pm SD) for continuous, normally distributed variables and median and interquartile range (IQR) for non-normally distributed variables. Standard errors (\pm SE) are given for heritability estimates. Unadjusted intrafamilial associations were estimated by calculating intraclass correlations (ICC) for sibpairs. The FCOR-program of the SAGE-software package (Case Western Reserve University, Cleveland, OH) was used with a uniform weighting scheme giving equal weights for each sibship regardless of the number of sib pairs within the sibships. (11) Similarly, the correlations between ordinal ETDRS-scores and retinopathy-status were also calculated with the FCOR-program using the same weighting scheme. Mean differences in current age and duration of diabetes between probands and siblings were calculated using a linear mixed model (Table 2.).

In order to study familial aggregation of proliferative retinopathy or any retinopathy three complementary analyses were used. First, the presence or absence of proliferative retinopathy or any retinopathy in the proband was estimated as a risk factor for the corresponding condition in the other siblings. The familial risks were estimated with logistic regression models, adjusted for conventional risk factors and fitted with generalized estimating equations using exchangeable correlation structure to account for correlations within sibships (12). Second, to measure the degree of concordance within sibships, the intraclass correlation of durations of diabetes to the diagnosis of proliferative retinopathy was calculated in the 29 sibships in which two siblings had proliferative retinopathy (Fig. 2). Third, the heritability (h^2)

of proliferative retinopathy was estimated by a liability threshold model as implemented in the SOLAR-software (SOLAR, Version 4.0.7. Southwest Foundation for Biomedical Research, San Antonio, TX) with HbA_{1c}, mean arterial pressure, gender and duration of diabetes as covariates. The liability threshold model is an extension of the variance components model to dichotomous traits, such as proliferative retinopathy (13). In the variance components model, the overall phenotypic variation is partitioned into individual variance components due to polygenic effects (multiple unmeasured genes under an additive variance), covariates (e.g. duration, gender, HbA_{1c}, blood pressure), and random environmental effects. The estimated heritability (h^2) is defined as the ratio of the genetic variance component to the residual phenotypic variance and is an estimate of the familiarity of the trait. The significance of the genetic component was determined by a likelihood ratio test. All other statistical calculations except the intraclass correlations and the variance component models were performed with SPSS 15.0 (SPSS, Chicago, IL).

RESULTS

Table 1 depicts the structure of the sibships and the availability of ophthalmic data. Table 2 shows the clinical characteristics of the studied patients and unadjusted intraclass correlations within sibships. Mean age at onset of diabetes was 14.3 (± 10.2) years. The male/female ratio was 202/167 and mean duration of diabetes 25.9 (± 11.8) years. The patient's highest ETDRS-score was achieved on a median of 2.1 (IQR -10.4 – (+) 1.0) years prior to the FinnDiane baseline visit. A strong positive association was found between the ETDRS-score and the nephropathy status ($r=0.63$, $P < 0.001$), which was available for 328 patients.

Proliferative retinopathy was found in 115/369 patients (31.1 % [95% CI 26.4-35.9]).

In 8/115 (7.0%) patients proliferative retinopathy was discovered at their first examination by an ophthalmologist. Thus there were no available reference points for these patients without proliferative retinopathy. The other patients ($n=107$) had all had at least one ophthalmic examination on a median of 1.0 (IQR -2.2 – (-) 0.4) years prior to the diagnosis. Detailed records of treatment and follow-up were available for each patient with proliferative retinopathy. Mean duration from onset of diabetes to proliferative retinopathy was 20.9 (± 7.5) years.

The familial risk of proliferative retinopathy was estimated in 182 siblings of 168 probands. Siblings of probands with proliferative retinopathy had higher unadjusted risk of proliferative retinopathy (Odds Ratio [OR] 4.07 [95% CI 2.06-8.07], $P < 0.001$), when compared to siblings of probands without proliferative retinopathy. When adjusted for duration of diabetes, HbA_{1c} and mean arterial pressure, proliferative retinopathy in the probands (48/168) remained a significant risk factor (OR 2.76 [1.25 - 6.11], $P=0.01$) for the corresponding condition in the siblings (61/182) (Table 3). In contrast, the absence of any retinopathy in the probands (37/168) was not associated with absence of any retinopathy in the siblings (39/182) of the probands (OR 2.0 [0.82 - 5.10], $P=0.13$). The absence of any retinopathy was associated with lower HbA_{1c} (OR 0.77 [0.59-0.99], $P=0.04$) and shorter duration of diabetes (OR 0.85 [0.78-0.92], $P < 0.001$), but not with blood pressure (OR 1.1 [0.98 – 1.06], $P=0.30$) or gender (OR 0.96 [0.36 - 2.53], $P=0.93$).

The 29 proband-sibling pairs in which both members had proliferative retinopathy were concordant for the survival time without proliferative retinopathy (ICC = 0.47 [0.14-0.71], $P=0.004$). (Fig.1). Despite a slightly shorter duration of diabetes (25.0 [± 11.8] vs. 26.8 [± 11.9] years, $P=0.15$), the younger

siblings had a higher prevalence of proliferative retinopathy (34.4% [66/192] vs. 27.7% [49/177], $p=0.17$) and often a shorter duration of diabetes to proliferative retinopathy (20.2 [± 7.0] vs. 21.7 [± 8.0] years, $P=0.17$) (Fig.1). In order to make sure these trends did not bias the estimates of familial risk, we further calculated the risk of proliferative retinopathy by designating the probands either randomly (OR 2.88 [1.32 – 6.27], $P=0.01$) or by designating the siblings with the longest duration as probands (2.48 [1.02-6.04], $p=0.04$). Thus, the selection of the oldest sibling as proband does not seem to produce a significant bias to the estimate of familial risk.

The heritability of proliferative retinopathy was $h^2=0.52$ (± 0.31 , $P<0.05$) in a sample of 362/396 patients. The gender of the patient was left out from the variance component model as being non-significant ($P>0.1$). The proportion of variance attributable to all covariates (HbA_{1c}, duration, blood pressure) was 0.23 (Kullback-Leibler R²).

DISCUSSION

This study shows an increased risk (OR 2.76 [1.25–6.11], $P=0.01$) of proliferative retinopathy in siblings of probands with proliferative retinopathy in type 1 diabetes. Such a familial clustering was supported by the estimated heritability of proliferative retinopathy $h^2 = 0.52$ (± 0.31 , $P<0.05$). Notably, this degree of familiarity is similar to the previously reported clustering for diabetic nephropathy in type 1 patients, and suggests that genes may play a major role also for the development of severe retinopathy. In previous studies regarding diabetic nephropathy roughly 50% of the risk could not be attributed to the familial clustering of conventional risk factors (14). Similarly, genetic risk factors may explain 50% of the risk of proliferative retinopathy.

Diabetic retinopathy continues to progress even after improvement of glycemic control (5;15). The more severe the retinopathy is, the longer the delay before a beneficial effect of improved glycemic control is observed. (5) Thus, retinopathy appears to have an inherent momentum of progression that by time leads to an almost linear increase in the incidence of proliferative retinopathy (2). Further proof of familiarity is the conspicuous concordance of the survival times within sibships (Fig. 2). Taken together, these findings may be consistent with an altered expression of one or more critical genes induced by hyperglycemia.

Previous studies have been able to show familial clustering of severe non-proliferative retinopathy in families with type 2 diabetes, (16;17) and in families with a mixture of both type 1 and type 2 patients (18). However, no studies have so far given estimates for the familial risk of proliferative retinopathy. Despite the familiarity of non-proliferative retinopathy, attempts to find evidence for an involvement of any major loci in diabetic retinopathy have turned out inconclusive. Three genome wide-scans have offered suggestive evidence of linkage, but on a number of different chromosomes in patients with type 2 diabetes (19-21). The associations to various biologically relevant candidate genes have been extraordinarily difficult to replicate (22). Such results are typical for multifactorial diseases with only a moderate familiarity. The genetic component of diabetic retinopathy is likely to be polygenic and does not exclude the importance of interacting environmental risk factors in the determination of the ultimate risk. Some environmental risk factors such as blood pressure and HbA_{1c} also appear to be determined at least in part by genetic factors. In this study, a single HbA_{1c}-measurement was a significant risk factor both in the logistic regression analysis as well as the heritability calculation, despite that patient's

highest ETDRS-score occurred on a median of 2.1 (IQR -10.4 – (+) 1.0) years prior to the date of the HbA_{1c} measurement in the FinnDiane –Study. This could be a reflection of the predictive value of biological, between-individual variations in HbA_{1c}, distinct from the mean blood glucose (23). In fact, it has been noted that a single HbA_{1c}-measurement offers a fair estimate of the glyceemic control during the previous ten years (24). Another significant risk factor in this study was blood pressure. Increased blood pressure is considered to be a multifactorial trait with an estimated genetic contribution in the range of 30-50 % (25). The present study may be limited by the fact, that the longitudinal changes in the risk factors could not be recorded, leaving possible residual intrafamilial correlations unaccounted for. However, it has been shown in a simulation study that familial clustering of two additive environmental risk factors only leads to a slight excess in the clustering of a disease among the siblings (26). Therefore, it is unlikely that the degree of familiarity observed here is the result of familial clustering of glyceemic control and blood pressure alone.

Microalbuminuria is a known predictor for the development of proliferative retinopathy in patients with type 1 diabetes (27). There is controversy whether this association is due to hyperglycaemia or whether nephropathy is truly an independent risk factor for proliferative retinopathy. It has been observed, that after renal transplantation or initiation of dialysis visual function stabilizes (28). The stabilization could also be due to other factors, such as lower blood pressure during renal replacement therapy (29). A strong positive association between the severity of retinopathy and the severity of nephropathy was noted in this study ($r=0.63$, $P<0.001$), which supports the hypothesis that there are common predisposing factors behind these two microvascular complications.

Retinal photography has been reported to be the most sensitive screening method for diabetic retinopathy. The sensitivity is in excess of 80% in detecting proliferative retinopathy (30). Ophthalmoscopy has less sensitivity, but conversely higher specificity. It provides good results in the hands of trained professionals such as ophthalmologists and diabetologists (30). A high percentage of patients with diabetes in Finland are undergoing regular fundus photography. The national guidelines for the screening of diabetic retinopathy were published already in 1992 and updated in 2006, (31) emphasizing fundus photography as the preferable screening method (32). The majority of the patients in this study had attended several screening examinations. Many were examined and treated by ophthalmologists and eventually 68% had fundus photographs available. Even with these repeated examinations, the absence or presence of any retinopathy was not found to cluster within families. This could reflect the fact that almost all patients with long enough duration of type 1 diabetes, will eventually develop some degree of retinopathy thus making the detection of familial clustering more difficult.

The FinnDiane Study is not by definition a population based study, which may limit the generalizability of the results. However, the possible selection bias is unlikely since the the geographic distribution of FinnDiane patients closely follows the distribution of the genetically homogeneous general population and also because we could obtain as much as 93 % of the ophthalmic data in the sibships. Furthermore, the treatment of diabetes and its complications is fairly uniform across Finland. The prevalence of proliferative retinopathy in this study (31.1 % [95% CI 26.4-35.9]) corresponds to the prevalence of 32.1 % [29.2 -35.0] in an independent sample of 1001 patients with a 24.2 (± 11.7) duration of diabetes in the

FinnDiane Study and to the prevalence of proliferative retinopathy (37.5 % [34.6 -40.4]) in a previous population based study of type 1 diabetes patients with similar duration of diabetes in Finland (33).

In conclusion, this study found a familial clustering of proliferative retinopathy in patients with type 1 diabetes, which cannot be accounted for by conventional risk factors. This suggests a significant genetic component in the pathogenesis of proliferative retinopathy.

ACKNOWLEDGMENTS

This study was supported by grants from Folkhälsan Research Foundation, Wilhelm and Else Stockmann Foundation, Finnish Eye Foundation, Eye and Tissue Bank Foundation, and a special governmental grant for health sciences research (TYH 3263). SAGE Software is supported by a U.S. Public Health Service Resource Grant (RR03655) from the National Center for Research Resources. We acknowledge all the physicians and nurses at each center participating in the collection of patients (see online appendix).

REFERENCES

1. Seaquist ER, Goetz FC, Rich S, Barbosa J: Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. *N Engl J Med* 320:1161-1165, 1989
2. Klein R: The epidemiology of diabetic retinopathy: findings from the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Int Ophthalmol Clin* 27:230-238, 1987
3. Deckert T, Simonsen SE, Poulsen JE: Prognosis of proliferative retinopathy in juvenile diabetics. *Diabetes* 16:728-733, 1967
4. Rossing K, Jacobsen P, Rossing P, Lauritzen E, Lund-Andersen H, Parving HH: Improved visual function in IDDM patients with unchanged cumulative incidence of sight-threatening diabetic retinopathy. *Diabetes Care* 21:2007-2015, 1998
5. DCCT Group: Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med* 342:381-389, 2000
6. UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:837-853, 1998
7. DCCT Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977-986, 1993
8. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 317:703-713, 1998
9. Fagerudd J, Forsblom C, Pettersson-Fernholm K, Groop PH: Implementation of guidelines for the prevention of diabetic nephropathy. *Diabetes Care* 27:803-804, 2004
10. Davis MD, Fisher MR, Gangnon RE, Barton F, Aiello LM, Chew EY, Ferris FL, III, Knatterud GL: Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study Report #18. *Invest Ophthalmol Vis Sci* 39:233-252, 1998
11. Keen KJ, Elston RC: Robust asymptotic sampling theory for correlations in pedigrees. *Stat Med* 22:3229-3247, 2003
12. Hanley JA, Negassa A, Edwardes MD, Forrester JE: Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol* 157:364-375, 2003

13. Duggirala R, Williams JT, Williams-Blangero S, Blangero J: A variance component approach to dichotomous trait linkage analysis using a threshold model. *Genet Epidemiol* 14:987-992, 1997
14. Krolewski AS, Fogarty DG, Warram JH: Hypertension and nephropathy in diabetes mellitus: what is inherited and what is acquired? *Diabetes Res Clin Pract* 39 Suppl:S1-14, 1998
15. Engerman RL, Kern TS: Progression of incipient diabetic retinopathy during good glycemic control. *Diabetes* 36:808-812, 1987
16. Hallman DM, Huber JC, Jr., Gonzalez VH, Klein BE, Klein R, Hanis CL: Familial aggregation of severity of diabetic retinopathy in Mexican Americans from Starr County, Texas. *Diabetes Care* 28:1163-1168, 2005
17. Rema M, Saravanan G, Deepa R, Mohan V: Familial clustering of diabetic retinopathy in South Indian Type 2 diabetic patients. *Diabet Med* 19:910-916, 2002
18. DCCT Group: Clustering of long-term complications in families with diabetes in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. *Diabetes* 46:1829-1839, 1997
19. Hallman DM, Boerwinkle E, Gonzalez VH, Klein BE, Klein R, Hanis CL: A genome-wide linkage scan for diabetic retinopathy susceptibility genes in mexican americans with type 2 diabetes from starr county, Texas. *Diabetes* 56:1167-1173, 2007
20. Imperatore G, Hanson RL, Pettitt DJ, Kobes S, Bennett PH, Knowler WC: Sib-pair linkage analysis for susceptibility genes for microvascular complications among Pima Indians with type 2 diabetes. Pima Diabetes Genes Group. *Diabetes* 47:821-830, 1998
21. Looker HC, Nelson RG, Chew E, Klein R, Klein BE, Knowler WC, Hanson RL: Genome-wide linkage analyses to identify Loci for diabetic retinopathy. *Diabetes* 56:1160-1166, 2007
22. Uhlmann K, Kovacs P, Boettcher Y, Hammes HP, Paschke R: Genetics of diabetic retinopathy. *Exp Clin Endocrinol Diabetes* 114:275-294, 2006
23. McCarter RJ, Hempe JM, Gomez R, Chalew SA: Biological variation in HbA1c predicts risk of retinopathy and nephropathy in type 1 diabetes. *Diabetes Care* 27:1259-1264, 2004
24. Barnas U, Schmidt A, Illievich A, Kiener HP, Rabensteiner D, Kaider A, Prager R, Abrahamian H, Irsigler K, Mayer G: Evaluation of risk factors for the development of nephropathy in patients with IDDM: insertion/deletion angiotensin converting enzyme gene polymorphism, hypertension and metabolic control. *Diabetologia* 40:327-331, 1997
25. Tanira MO, Al Balushi KA: Genetic variations related to hypertension: a review. *J Hum Hypertens* 19:7-19, 2005
26. Khoury MJ, Beaty TH, Liang KY: Can familial aggregation of disease be explained by familial aggregation of environmental risk factors? *Am J Epidemiol* 127:674-683, 1988

27. Mathiesen ER, Ronn B, Storm B, Foght H, Deckert T: The natural course of microalbuminuria in insulin-dependent diabetes: a 10-year prospective study. *Diabet Med* 12:482-487, 1995
28. Laatikainen L, Summanen P, Ekstrand A, Groop L: Ophthalmological follow-up of diabetic patients after kidney transplantation. *Ger J Ophthalmol* 2:24-27, 1993
29. Watanabe Y, Yuzawa Y, Mizumoto D, Tamai H, Itoh Y, Kumon S, Yamazaki C: Long-term follow-up study of 268 diabetic patients undergoing haemodialysis, with special attention to visual acuity and heterogeneity. *Nephrol Dial Transplant* 8:725-734, 1993
30. Hutchinson A, McIntosh A, Peters J, O'Keefe C, Khunti K, Baker R, Booth A: Effectiveness of screening and monitoring tests for diabetic retinopathy--a systematic review. *Diabet Med* 17:495-506, 2000
31. Summanen P, Kallioniemi V, Komulainen J, Lamminen H, Levanen H, Orhanen E, Tulokas S, Virtamo T, von Wendt G: Diabetic retinopathy. Current care guideline. *Duodecim* 123:421-422, 2007
32. Retinopathy Working Party: A protocol for screening for diabetic retinopathy in Europe. *Diabet Med* 8:263-267, 1991
33. Virtamo T, Summanen P, Tuomilehto J, Laatikainen L: Diabetic retinopathy and visual impairment in juvenile onset diabetics in Finland. 11th Meeting of the European Association for the Study of Diabetic Eye Complications (EASDEC). Paris, France. May 18-20, 2001. (Abstract). *Diabetes Metab* 27 Suppl 2, 2001

Table 1. Structure of sibships.

Siblings with type 1 diabetes in the same family	Families	Patients with type 1 diabetes	Ophthalmic data available	Patients with proliferative retinopathy
2 siblings	171	342	323	101
3 siblings	14	42	38	13
4 siblings	3	12	8	1
Total	188	396	369	115

Table 2. Clinical characteristics and concordance within sibships (intraclass correlations) for the siblings with type 1 diabetes (n=396).

Variable	Mean (\pm SD)	Minimum - Maximum	Intraclass correlation (95 %CI)
Age at onset (years) (n=387)	14.3 (\pm 10.2)	0.2-40.0	0.15 (0.02-0.21)
Duration of diabetes (years) at the latest ophthalmic examination (n=369)	25.9 (\pm 11.8)	1.0-55.4	0.39 (0.26-0.45)
Difference of duration between probands and siblings (years)	2.4 (\pm 1.3) ^{¶¶}		
Current age (years) (n=387)	40.2 (\pm 11.5)	14.5-69.3	0.69 (0.61-0.73)
Age difference between proband and siblings (years)	4.9 (\pm 1.2) ^{¶¶}		
HbA _{1c} (%) (n=380)	8.5 (\pm 1.5)	5.0-13.8	0.22 (0.09-0.29)
Systolic pressure (mmHg) (n=378)	135 (\pm 18)	95-215	0.20 (0.07-0.27)
Diastolic pressure (mmHg) (n=378)	80 (\pm 9)	50-113	0.10 (-0.04-0.16)
MAP (mmHg) (n=378)	100 (\pm 12)	72-140	0.18 (0.04-0.25)
BMI (kg/m ²) (n=354)	25.3 (\pm 3.9)	16.2-43.0	0.21 (0.07-0.28)
Total cholesterol (mmol/l) (n=341)	4.9 (\pm 1.0)	1.9-12.0	0.21 (0.06-0.30)
HDL-cholesterol (mmol/l) (n=341)	1.6 (\pm 0.52)	0.2-4.3	0.33 (0.18-0.40)
Current smoking (n=369)	Yes No	86 (23%) 83 (77%)	0.15 (0.01-0.22)
ETDRS-score (n=369)	40* (IQR 20-62)	10-80	0.37 (0.24-0.43)
PDR (yes/no) (n=369)	Yes 115 (31%) No 254 (69%)		0.28 (0.14-0.35)
Nephropathy status (n=328)	Normoalbuminuria 202 (54%) Microalbuminuria 51 (14%) Macroalbuminuria 50 (14%) End stage renal disease 25 (7%)		0.26 (0.06-0.36)

¶ Standard error of mean difference, * Median value, SD = Standard deviation, CI= Confidence Interval, IQR= Interquartile Range, PDR=Proliferative Retinopathy, BMI = Body Mass Index, MAP= Mean Arterial Pressure, 188 sibships, male/female 202/167.

Table 3. Familial risk of proliferative retinopathy. The presence of proliferative retinopathy in the proband was used as risk factor for proliferative retinopathy in 182 siblings of 168 probands in a logistic regression analysis.

Variable	OR (95 % CI)	β (SE)	P-value
Proband's PDR – status (yes/no)	2.76 (1.25-6.11)	1.02 (0.40)	0.01
MAP (mmHg)	1.03 (0.99-1.06)	0.02 (0.17)	0.15
HbA _{1c} (%)	1.33 (1.03-1.73)	0.29 (0.14)	0.03
Duration of diabetes (years)	1.13 (1.08-1.17)	0.12 (0.02)	< 0.001
Male gender	1.12 (0.51-2.45)	0.12 (0.40)	0.8

MAP= Mean arterial blood pressure, PDR= Proliferative Diabetic Retinopathy, OR=Odds Ratio

Figure 1. Concordance within sibship (intraclass correlation) of survival time without proliferative retinopathy in the 29 sibpairs in which both members had proliferative retinopathy (ICC = 0.47 [95% CI 0.14-0.71], P=0.004).

